Trials

SCORE-IT - Selecting Core Outcomes for Randomised Effectiveness trials In Type 2 Diabetes. A Systematic Review of Registered Trials.

--Manuscript Draft--

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Abstract:	Background: Outcomes measured in clinical trials should be meaningful to patients, health care professionals and researchers, yet there is heterogeneity in the outcomes used across trials. This inconsistency impacts on the ability to compare findings and may mean that the results have little importance to health care professionals and the patients that they care for. The aim of the present study is to review the outcomes used in registered trials of therapies for type 2 diabetes mellitus as the first step in the development of a core outcome set for effectiveness trials in type 2 diabetes. Materials and methods: A systematic review of clinicaltrials.gov entries was completed for randomised, open (actively recruiting or in follow up period), phase 3 and 4 trials of type 2 diabetes mellitus in adults. Trials of; the treatment of diabetes complications; co-morbidities; prevention; and surgery were excluded. Each trial was screened for eligibility and outcomes extracted from the primary and secondary outcomes data fields and free text study information. The outcomes were recorded verbatim and classified into core outcome domains according to the COMET taxonomy. Results: 354 trial registrations were reviewed for eligibility and 138 trials included. A total of 1444 outcomes were extracted with a median of 8 outcomes per trial (range 1-60). Outcomes were categorised into 30 different outcome domains according to the COMET taxonomy, but no single domain or outcome was measured in 100% of trials. The majority of trials (88%) included outcomes in the "metabolism and nutrition" domain, such as, lipids and lipoproteins (21%), HbA1c (18%), hypoglycaemia (14%), fasting plasma/blood glucose (11%), glycaemic variability (8%), postprandial response (8%) and insulin sensitivity (5%). Only 10% of trials included one or more patient reported outcomes, of these 29% included the Diabetes Treatment Satisfaction Questionnaire. Conclusions: There is marked heterogeneity in the outcomes measured in registered therapeutic intervention trials for type 2 diabetes. The use of an agreed set of core outcomes will improve the consistency of reporting in clinical trials for type 2 diabetes. Registration: The core outcome set study, of which this is a part, is registered in the COMET database, http://www.comet-initiative.org/studies/details/956.
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Response to Reviewers:	Thank you to the reviewers and the editor for their comments and quick review of the manuscript. We have addressed specific points below and in the manuscript. From the editor: We wish for there to be a more robust discussion of the choice of the single database. You can elect to either adjust your manuscript, or simply put it as a response - although I would prefer the former. Response: We have revised the manuscript discussion to include the benefits and rationale of using a single database. In the field of diabetes where there is a wealth of published studies we feel that a focused approach to identify currently used outcomes is an efficient use of resources and yet will still yield a rich and relevant list of outcomes. We have generated a search strategy for use in other databases and a MEDLINE search has yielded 15500 publications in the last 10 years. Review of this number of abstracts for eligibility followed by full text review and data extraction is a substantial task that would be unlikely to generate additional meaningful outcome data. Our use of a single database allows identification of current and relevant outcomes as these are those used in current open trials rather than those that were designed several years ago and completed recently. Reviewer #2: In general, given the relevance of the topic, it would be great if authors had searched in other databases (e.g., Medline and Embase). I don´t see the reason because authors only searched in the clinicaltrial.gov website. They mentioned this is the first step, but it is not clear what they will do for the second or the following steps. This is the main weakness of this manuscript. Response: See above for the response regarding the search strategy. This manuscript focuses on the first step of development of a core outcomes set for trials in type 2 diabetes, which is identification of an outcomes list for use in an online Delphi survey; this is described in the final discussion but we have also added an additional reference to the COMET handbook on line 33 which describes the steps in core outcome set development. It would be good if the authors explain why they searched for COS from 21st October 2016 27 and 14-September 2017. It seems a little bit odd this dates. Response: The manuscript text has been amendment to clarify that the database was searched prior to commencing work and prior to manuscript submission rather than a search between these two dates.
Additional Information:	
Question	**Response**
Is this study a clinical trial?<hr>A clinical trial is defined by the Word Health Organisation as ‘any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes’.	No

SCORE-IT - Selecting Core Outcomes for Randomised Effectiveness trials In Type 2 Diabetes. A Systematic Review of Registered Trials.

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Abstract

Background: Outcomes measured in clinical trials should be meaningful to patients, health care professionals and researchers, yet there is heterogeneity in the outcomes used across trials. This inconsistency impacts on the ability to compare findings and may mean that the results have little importance to health care professionals and the patients that they care for. The aim of the present study is to review the outcomes used in registered trials of therapies for type 2 diabetes mellitus as the first step in the development of a core outcome set for effectiveness trials in type 2 diabetes.

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Materials and methods: A systematic review of clinicaltrials.gov entries was completed for randomised, open (actively recruiting or in follow up period), phase 3 and 4 trials of type 2 diabetes mellitus in adults. Trials of; the treatment of diabetes complications; co-morbidities; prevention; and surgery were excluded. Each trial was screened for eligibility and outcomes extracted from the primary and secondary outcomes data fields and free text study information. The outcomes were recorded verbatim and classified into core outcome domains according to the COMET taxonomy.

Results: 354 trial registrations were reviewed for eligibility and 138 trials included. A total of 1444 outcomes were extracted with a median of 8 outcomes per trial (range 1-60). Outcomes were categorised into 30 different outcome domains according to the COMET taxonomy, but no single domain or outcome was measured in 100% of trials. The majority of trials (88%) included outcomes in the "metabolism and nutrition" domain, such as lipids and lipoproteins (21%), HbA1c (18%), hypoglycaemia (14%), fasting plasma/blood glucose (11%), glycaemic variability (8%), postprandial response (8%) and insulin sensitivity (5%). Only 10% of trials included one or more patient reported outcomes, of these 29% included the Diabetes Treatment Satisfaction Questionnaire.

Conclusions: There is marked heterogeneity in the outcomes measured in registered therapeutic intervention trials for type 2 diabetes. The use of an agreed set of core outcomes will improve the consistency of reporting in clinical trials for type 2 diabetes.

Registration: The core outcome set study, of which this is a part, is registered in the COMET database, http://www.comet-initiative.org/studies/details/956.

Keywords

Core outcome set, systematic review, type 2 diabetes

Background (150-200)

Type 2 diabetes mellitus accounts for over 90% of all diabetes. It is characterised by abnormal glucose metabolism brought about by resistance to insulin action and an inadequate compensatory insulin secretory response [1, 2]. The resulting hyperglycaemia, if left untreated, can lead to both macrovascular and microvascular complications which may be further exacerbated by obesity, elevated blood pressure, and dyslipidaemia that are also often associated with type 2 diabetes mellitus. [3]

Systematic reviews of glucose lowering treatments for type 2 diabetes have identified inconsistency in the outcomes measured and reported and whilst many routinely report glycated haemoglobin, other measures of glycaemic control and outcomes relating to hypoglycaemia, mortality, diabetes-related complications and quality of life are less frequently reported if at all. [3-8]. The heterogeneity in the outcomes used may impact on the translatability of trials into benefits for patients [9, 10]. The World Health Organisation International Classification of Functioning, Disability and Health (ICF) core set for diabetes mellitus contains 85 second level categories; 28 of these are included in the brief ICF core set that the ICF state can be used for the assessment of patients with diabetes participating in a clinical trial [11, 12]. However, not only is it impractical to measure all 28 outcomes in the brief ICF core set in all trials, there is also an issue that it just includes outcomes related to function. Using only the brief ICF core set in clinical trials could mean that other outcomes important to patients and healthcare professionals, are not measured.

One suggestion to improve the relevance and consistency of trial outcomes includes the development of a Core Outcome Set (COS), that represents the minimum set of outcomes that should be measured and reported in any clinical trial for a given condition, in this case type 2 diabetes[13-15]. To ensure that no COS for trials of type 2 diabetes existed or was in development by another group a review of entries in the Core Outcome Measures in Effectiveness Trials (COMET)

initiative database was completed prior to commencing this project ([16], ~~searched~~ on 21st October 2016 and again prior to manuscript submission on 14-September 2017). No published or ongoing COS for the treatment of type 2 diabetes without co-morbidity was identified (additional file 1).

Here we aim to describe the outcomes used in trials, ~~-~~currently recruiting, ~~evaluating~~ that evaluate therapeutic interventions for type 2 diabetes, registered in a large international public clinical trial registry, as the first step in the development of a COS for type 2 diabetes [15].

Methods

Search strategy

On the 20th October 2016 the ClinicalTrials.gov database ([17]) was searched using the following search terms: Type 2 diabetes-Type II diabetes – non-insulin dependent diabetes- Open studies - Interventional studies - Phase 3, 4 - Studies received from 10/11/2007.

In the context of the clinicaltrials.gov registry, an "open" study is one that is currently recruiting participants or will be recruiting participants in the future.

Clinicaltrials.gov was chosen as this registry allows outcomes to be easily identified and extracted and was the main source of trials in a previous study using trial registries to identify outcomes[7]. Trials registered prior to 10/11/2007 have been reported elsewhere [7].

Eligibility Criteria

Phase 3 and 4 trials of therapeutic interventions for patients with type 2 diabetes were included**.** Trials were excluded if they met any of the following criteria: Phase 1 and 2 trials (including entries listed as phase 2/phase 3); prevention trials; trials of treatment for diabetic foot ulcers, diabetic

retinopathy, or for diabetic nephropathy; trials of bariatric surgery, and trials of treatment for any other co-morbidity including non-alchoholic fatty liver disease and cardiovascular disease (trials assessing cardiovascular safety of glucose lowering drugs are eligible for inclusion). When trials were registered more than once, only the initial registration was included.

Assessment of Trial Eligibility

NH and RJ reviewed the first 40 trials together with full discussion about inclusion and exclusion of trials and outcome extraction. A further 5% of trials was then randomly selected and independently reviewed in parallel by the reviewers to ensure consistency. Where disagreement was noted the reviewers discussed the study before reaching a decision. No study required third reviewer arbitration.

Data extraction

Data on study characteristics was extracted by NH that included trial phase, region, design, type of intervention (pharmaceutical, nutritional, educational/lifestyle or device) and duration of follow up. Data on outcomes listed in the clinicaltrials.gov protocol registration entry was extracted by NH and RJ from the specific outcomes fields and from the study information free text. Where composite outcomes were used, all component outcomes were included. Where an outcome was reported in terms of the measurement instrument used, for example a particular questionnaire, the instrument was reviewed and outcomes extracted.

Outcome Classification

NH categorised each outcome according to the COMET taxonomy of core domains [submitted for publication]. This taxonomy comprises 38 domains under five areas (death, physiological/clinical, life impact, resource use and adverse events). Functional outcomes were also categorised according to the ICF top level domains [18]. A random check of categorisation was completed on 30% of

outcomes by JW, discrepancies were resolved through consensus and discussion with a third reviewer (PRW) where necessary.

Results

Search results and study characteristics

The search returned 675 entries in the clinicaltrials.gov database, and after duplicates were removed 354 trials were screened for eligibility, of which 138 were included (trial registration numbers of included trials are available in additional file 2). The flow of included trials is shown in Figure 1.

Of the 138 eligible trials, 127 (92%) were trials of drug interventions with the remainder evaluating educational or lifestyle (4%), nutritional (2%) or device (1%) interventions. The majority (65%) were phase 4 trials with 200 participants or less (median 135, range 12-5000) and follow up of 6 months of less (median 24 weeks, range 0- 364 weeks). Characteristics of included trials are described in Table 1.

Classification of trial outcomes

COMET taxonomy

A total of 1444 individual outcomes were extracted with a median of 8 outcomes per trial (range 1-60). Each outcome was reviewed and categorised using the COMET taxonomy (Table 2).

The most frequently included domain was “metabolism and nutrition” with 87% of trials measuring one or more outcomes in this domain and 92 (67%) trials including an outcome from this domain as their primary outcome. The key outcomes included in “metabolism and nutrition” were: outcomes related to lipids and lipoproteins (21%), HbA1c (18%), hypoglycaemia (14%), fasting plasma/blood glucose (11%), glycaemic variability (8%), postprandial response (8%) and insulin sensitivity (5%). The remaining 21% of outcomes were varied and included markers of oxidative and nitrosative stress, gut hormones, energy expenditure and other non-specific metabolic markers.

Nearly half of the studies (47%) included outcomes categorised as “general outcomes” (outcomes that affect the whole body and cannot be attributed to a certain body system) which included outcomes related to body weight (42%), adiposity (17%), other anthropometric measures (11%), clinical chemistry not attributed to one particular body function or system (11%), physical activity (5%), fatigue (3%) and non-specific pain (3%). The remaining 10% of outcomes in the “general outcomes” category included vital signs, non-specific patient reported outcomes (those with no detail provided in the clinicaltrials.gov entry other than ‘patient reported outcome’), general health, smoking status, morbidity and global effectiveness.

Use of Patient Reported Outcome Measures

Fourteen (10%) studies listed one or more patient reported outcome measures (PROMs). Twenty three PROMs were identified which measured 68 outcomes (table 3). The use of PROMs was varied and of the 23 PROMs, 87% were used in only one study. The most frequently used PROM was the Diabetes Treatment Satisfaction Questionnaire used by four (29%) of the studies reporting PROMs.

ICF core set and outcomes used in registered trials

Of the 1444 individual outcomes, 80 (5.5%) did not fit with any of the ICF categories. These outcomes included unspecified adverse events (n=44), treatment preference or satisfaction (n=5), mortality (n=2), pharmacokinetics (n=1) and general physiological or laboratory measures (n=27). Ten categories in the ICF brief set and an additional 46 categories in the ICF full core set were not associated with any outcomes being measured in the trials. The breakdown of outcomes according to the ICF core set is provided in additional files 3 and 4).

Discussion

There is heterogeneity in the outcomes used across registered open trials for type 2 diabetes. Whilst some outcomes are commonly measured, and are expected in trials that aim to treat

hyperglycaemia, there is no consensus on which outcomes should be routinely measured and reported, with no single outcome or outcome domain being measured in all trials.

Reaney et al have recently reviewed PROMs used in published phase 3 type 2 diabetes mellitus trials of GLP-1 receptor agonists, novel insulins, SGLT-2 inhibitors, and DPP-4 inhibitors [19]. The identified PROMs in the included studies were mixed and varied compared to those identified in the present review, with overlap of only four measurement instruments (DTSQ, EQ5D, SF-36 and HFS-11 worry scale). The diabetes treatment satisfaction questionnaire (DTSQ) was the most frequently used PROM in both the review by Reaney et al and in the present study which may be due to the recommendations made by the World Health Organisation (WHO) to encourage psychological wellbeing in patients with diabetes[20]. In the present study only 10% of trials included a PROM; this is comparable with the study by Barsdorf *et al* in 2012 who found that only 7.5% of phase 3 pharmaceutical interventions for type 2 diabetes, registered with clinical trials.gov, included a PROM [21]. Gandhi *et al* [7] considered patient important outcomes in registered trials, described as outcomes that affect the way patients feel, function or survive [8]. In the present study over half (51%) of trials included one or more outcomes meeting this definition. However, this definition was not developed with input from patients with type 2 diabetes and so may not truly reflect outcomes of treatment that they consider to be the most important.

A limitation of the present study is that only one trials registry, clinicaltrials.gov, has been used. However, in the study by Gandhi et al clinicaltrials.gov was the main registry source accounting for 81% of included studies [7]. In this study only open (actively recruiting or will recruit in the near future) trials have been included representing the current use of outcomes in trials treating hyperglycaemia in patients with type 2 diabetes mellitus. Including only open trials has the advantage that the outcomes used reflect the current state of affairs in a particular research area. In a topic area as vast as type 2 diabetes this has additional importance of not only the resource needed to review studies and generate an outcomes list but also ensuring that the outcomes

included in a subsequent Delphi survey are relevant and do not represent outdated and redundant outcomes.

A number of core outcome sets exist for type 2 diabetes mellitus in clinical practice but these too display heterogeneity in included outcomes [22]. The ICF core outcome set [12] was developed using a consensus process, and was designed for use in clinical practice although it has been suggested that the brief set of 28 items is suitable for use in clinical trials. However, the ICF set of 28 outcomes is impractical for use as a COS due to the large number of outcomes and the focus solely on function which may mean that it does not contain other outcomes important to patients with diabetes and health professionals caring for them.

This review of current registered trials highlights the need for a COS for use in clinical trials of type 2 diabetes; it ~~and~~ will contribute to a preliminary list of outcomes and outcome domains for use in the first round of an online Delphi survey to identify which outcomes are of importance to researchers, health care professionals and patients.

Abbreviations

COMET – Core Outcome Measures in Effectiveness Trials

COS - Core Outcome Set

DPP-4 - Dipeptidyl peptidase-4

DTSQ – Diabetes Treatment Satisfaction Questionnaire

GLP-1 - Glucagon-like peptide 1

HbA1c – Glycated haemoglobin

ICF - International Classification of Functioning, Diasbility and Health

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PROM – Patient Reported Outcome Measure

SGLT 2 – Sodium-glucose co-transporter 2

WHO- World Health Organisation

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. Data relating to included entries in the clinical trials.gov registry is provided in additional file 1.

Competing interests

PRW is member of the COMET Management Group and co-applicant on grants to support COMET and related work.

Funding

This work has received funding from the European Union's Horizon 2020 research and innovation programme (CORBEL, under grant agreement n° 654248)

Authors' contributions

PRW, NH and RJ conceived and designed the study. NH, RJ and PRW performed the search and extracted outcomes. NH, JW and PRW reviewed and categorised outcomes. NH drafted the manuscript; all authors reviewed and approved the manuscript.

Collaborating authors, part of the SCORE-IT Study Team: Serena, Battaglia, Jacques Demotes-Mainard, Valerie Gailus-Durner, Silvio Garattini, Cecilia AC Prinsen, Michael Raess, Patricia da Silva-Buttkus, Caroline B Terwee,

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Additional Files

Additional file 1. Summary of diabetes research on COMET database .doc

Additional file 2. List of all included studies .xls

Additional file 3. Review of outcomes against the ICF core set. .doc

Supplementary 4. ICF codes not used in outcomes.xlsx

Tables

Table 1 Description of included trials

	N (%)
Year	
2009	1 (1)
2010	0 (0)
2011	2 (1)
2012	3 (2)
2013	6 (4)
2014	21 (15)
2015	49 (36)
2016	56 (41)
Phase	
3	48 (35)
4	90 (65)
Planned enrolment (median and range)	135 (12 5000)
Region of work[a]	
Asia	55 (40)
Europe	45 (33)
North America	46 (33)
South America	8 (6)
Africa	6 (4)
Central America	4 (3)
Australia	1 (1)
Not reported	6 (4)
Trial design	
Parallel	125 (91)
Crossover	11 (8)

Other	2 (1)
Type of intervention	
Drug	137 (92)
Placebo	83 (60)
Active drug	36 (26)
Usual care	1 (1)
Other	7 (5)
Education or lifestyle	3 (2)
Nutrition	6 (4)
Device	2 (1)
Duration of follow up (median and range)[b]	24 (0-364) weeks
[a]Number exceeds total as a number of studies were conducted across multiple geographical areas. [b]0 Weeks = <24 hour follow up (n=3)	

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Table 2. Summary of outcomes categorised according to the COMET taxonomy

Core area	**Core domains**	Number of trials including one or more outcome in core domain (%)	Number of outcomes included in core domain (%)	Number of trials including as a primary outcome[a]
Death	Mortality/survival	3 (2.2)	3 (0.2)	0
Physiological/ clinical	Blood and lymphatic system outcomes	9 (6.5)	19 (1.3)	1
	Cardiac outcomes	20 (14.5)	56 (3.9)	9
	Congenital, familial and genetic outcomes	0(0)	0 (0)	
	Endocrine outcomes	31(22.5)	50 (3.5)	7
	Ear and labyrinth outcomes	0 (0)	0 (0)	0
	Eye outcomes	2 (1.4)	2 (0.1)	0
	Gastrointestinal outcomes	5 (3.6)	20 (1.4)	2
	General outcomes	65 (47.1)	146 (10.1)	3
	Hepatobiliary outcomes	12 (8.7)	25 (1.7)	3
	Immune system outcomes	28 (20.3)	73 (5.1)	4
	Infection and infestation outcomes	4 (2.9)	8 (0.6)	0
	Injury and poisoning outcomes	0 (0)	0 (0)	0
	Metabolism and nutrition outcomes	121 (87.7)	582 (40.3)	92
	Musculoskeletal and connective tissue outcomes	2 (1.4)	2 (0.1)	1
	Outcomes relating to neoplasms: benign, malignant and unspecified (including cysts and polyps)	0 (0)	0 (0)	0
	Nervous system outcomes	6 (4.3)	16 (1.1)	2
	Pregnancy, puerperium and perinatal outcomes	0 (0)	0 (0)	0
	Renal and urinary outcomes	27 (19.6)	76 (5.3)	5
	Reproductive system and breast	0 (0)	0 (0)	0

Table 2. Summary of outcomes categorised according to the COMET taxonomy

Core area	Core domains	Number of trials including one or more outcome in core domain (%)	Number of outcomes included in core domain (%)	Number of trials including as a primary outcome[a]
	outcomes			
	Psychiatric outcomes	2 (1.4)	2 (0.1)	0
	Respiratory, thoracic and mediastinal outcomes	3 (2.2)	11 (0.8)	1
	Skin and subcutaneous tissue outcomes	1 (0.7)	1 (0.1)	0
	Vascular outcomes	51 (37)	134 (9.3)	13
	Physical functioning	5 (3.6)	7 (0.5)	0
Life impact	Social functioning	5 (3.6)	6 (0.4)	0
	Role functioning	3 (2.2)	6 (0.4)	0
	Emotional functioning/wellbeing	8 (5.8)	28 (1.9)	0
	Cognitive functioning	2 (1.4)	22 (1.5)	0
	Global quality of life	4 (2.9)	5 (0.3)	0
	Perceived health status	4 (2.9)	4 (0.3)	0
	Delivery of care	30 (21.7)	60 (4.2)	4
	Personal circumstance	0 (0)	0 (0)	0
Resource use	Economic	4 (4)	6 (0.4)	0
	Hospital	3 (2.2)	4 (0.3)	0
	Need for intervention	16 (11.6)	24 (1.7)	1
	Societal/carer burden	0 (0)	0 (0)	0
Adverse Events	Adverse events/effects	33 (23.9)	46 (3.2)	5

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Table 3. Summary of Patient Reported Outcome Measures used

		Diabetes satisfaction with treatment (DTSQ and DTSQc)	SF-36	Diabetes distress scale	Summary of diabetes self-care activities	Diabetes self-care activities scale.	8 item Morisky Medication Adherence Scale	Basic activities of daily living	Cognitive Instrumental Activities of Daily Living Scale (Cog-IADL)	Diabetes empowerment scale	Diabetes Quality of Life (DQOL)	EQ5-D	Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)	Global Clinical Dementia Rating	HFS-11 worry scale	Hospital anxiety and depression	Hypoglycaemia patient questionnaire	international physical activity questionnaire	Mini Mental State Examination (MMSE)	Montreal Cognitive Assessment scale (MoCA)	Patient Health Questionnaire-2	Subjective Memory and Cognitive Complaint (SMCC)	Well Being questionnaire Short Form (W-BQ12)	WHO-5	Number of PROMs measuring outcome
	Number of trials using PROMs	4	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-
Core domains	**Outcomes measured by PROM**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gastrointestinal outcomes	Nausea/vomiting												X												1
	Fullness/early satiety												X												1
	Bloating												X												1
General outcomes	Pain	-	X	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	2
	General health	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Metabolism and nutrition outcomes	Symptomatic hypoglycaemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	1
	Asymptomatic hypoglycaemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	1
Physical	Mobility											X													1

Functioning	Physical functioning		x																														1
	Energy/fatigue		x																														2
	Physical activity																				1												1
	Activities of daily living							x	x																								2
	Usual activities											x																					1
	Managing the psychosocial aspects of diabetes	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
	Quality of Life- social/vocational concerns										x																						1
Social functioning	Social functioning		x							x																							2
	Quality of Life- general interest	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x					1
	Role limitations due to physical health		x																														1
Role functioning	Role limitations due to emotional problems		x																														1
	Dissatisfaction and readiness to change	-	-	-	-	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
	Setting and achieving goals									x																							1
	Emotional burden			x																													1
	Regimen distress			x																													1
	Interpersonal distress			x																													1
	Physician distress			x																													1
	Anxiety											x					x																2
	Depression											x					x							x								3
	Worries about diabetes										x																						1
	Emotional wellbeing		x																														1
	Mood																														x		1
	Vitality																														x		1
	Negative wellbeing																													x			1
	Positive wellbeing																													x			1
Emotional functioning/ wellbeing	General well being																													x			1
	Fear of hypoglycaemia - behaviour															x																	1
	Fear of hypoglycaemia - worry	-	-	-	-	-	-	-	-	-	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
	Orientation													x							x	x											3
	Registration																				x												1
Cognitive functioning	Attention and calculation																				x												1
	Recall																				x												1

	~~Language~~																		~~X~~	~~X~~					~~2~~
	~~Attention and concentration~~																			~~X~~					~~1~~
	~~Executive functions~~																			~~X~~					~~1~~
	~~Memory~~													~~X~~						~~X~~					~~2~~
	~~Visuoconstructional skills~~																			~~X~~					~~1~~
	~~Conceptual thinking~~																			~~X~~					~~1~~
	~~Calculations~~																			~~X~~					~~1~~
	~~Judgement and problem solving~~													~~X~~											~~1~~
	~~Community affairs~~													~~X~~											~~1~~
	~~Home and hobbies~~													~~X~~											~~1~~
	~~Personal care~~													~~X~~											~~1~~
	~~Subjective memory~~																					~~X~~			~~1~~
	~~Cognitive complaint~~	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	~~X~~	-	-	~~1~~
~~Global Quality of Life~~	~~Quality of Life -life satisfaction~~										~~X~~														~~1~~
	~~Quality of Life – diabetes impact~~										~~X~~														~~1~~
~~Perceived health status~~	~~Perceived blood glucose control~~	~~X~~	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	~~1~~
	~~Self-Care Activities - general diet~~				~~X~~	~~X~~																			~~2~~
	~~Self-Care Activities – specific diet~~				~~X~~	~~X~~																			~~2~~
	~~Self-Care Activities – medication taking~~				~~X~~																				~~1~~
	~~Self-care Activities - blood glucose testing~~				~~X~~	~~X~~																			~~2~~
	~~Self-Care Activities – exercise~~				~~X~~	~~X~~																			~~2~~
	~~Self-Care Activities - foot care~~				~~X~~	~~X~~																			~~2~~
	~~Self-Care Activities - smoking~~				~~X~~	~~X~~																			~~2~~
	~~Self-Care - unspecified~~											~~X~~													~~1~~
	~~Satisfaction with treatment~~	~~X~~																							~~1~~
	~~Patient knowledge of treatment for hypoglycaemia~~															~~X~~									~~1~~
	~~Medication adherence~~						~~X~~																		~~1~~
~~Delivery of Care~~	~~Patient knowledge driving and hypoglycaemia~~		-	-	-	-	-	-	-	-	-	-	-	-	-	-	~~X~~	-	-	-	-	-	-	-	~~1~~

~~Figure Legends~~

~~Figure 1. Flow chart of included trials.~~

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Additional Files

Additional file 1. Summary of diabetes research on COMET database .doc

Additional file 2. List of all included studies.xls

Additional file 3. Review of outcomes against the ICF core set. .doc

Supplementary 4. ICF codes not used in outcomes.xlsx

PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Included in abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3 and 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Risk of bias was not assessed as the focus was on outcome extraction only.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable for this review.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4 (for outcomes only)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable for this review.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable for this review.

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Included in figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Provided in table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable for this review of outcomes used.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Meta analysis not completed.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable for this review.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable for this review.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Not applicable for this

			review.
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 8.
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Pages 7,8,9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table 1 Description of included trials	
	N (%)
Year	
2009	1 (1)
2010	0 (0)
2011	2 (1)
2012	3 (2)
2013	6 (4)
2014	21 (15)
2015	49 (36)
2016	56 (41)
Phase	
3	48 (35)
4	90 (65)
Planned enrolment (median and range)	135 (12-5000)
Region of work[a]	
Asia	55 (40)
Europe	45 (33)
North America	46 (33)
South America	8 (6)
Africa	6 (4)
Central America	4 (3)
Australia	1 (1)
Not reported	6 (4)
Trial design	
Parallel	125 (91)
Crossover	11 (8)
Other	2 (1)
Type of intervention	
Drug	137 (92)
Placebo	83 (60)
Active drug	36 (26)
Usual care	1 (1)
Other	7 (5)
Education or lifestyle	3 (2)
Nutrition	6 (4)
Device	2 (1)
Duration of follow up (median and range)[b]	24 (0-364) weeks
[a]Number exceeds total as a number of studies were conducted across multiple geographical areas. [b]0 Weeks = <24 hour follow up (n=3)	

Table 2. Summary of outcomes categorised according to the COMET taxonomy				
Core area	**Core domains**	Number of trials including one or more outcome in core domain (%)	Number of outcomes included in core domain (%)	Number of trials including as a primary outcome[a]
Death	Mortality/survival	3 (2.2)	3 (0.2)	0
Physiological/ clinical	Blood and lymphatic system outcomes	9 (6.5)	19 (1.3)	1
	Cardiac outcomes	20 (14.5)	56 (3.9)	9
	Congenital, familial and genetic outcomes	0(0)	0 (0)	
	Endocrine outcomes	31(22.5)	50 (3.5)	7
	Ear and labyrinth outcomes	0 (0)	0 (0)	0
	Eye outcomes	2 (1.4)	2 (0.1)	0
	Gastrointestinal outcomes	5 (3.6)	20 (1.4)	2
	General outcomes	65 (47.1)	146 (10.1)	3
	Hepatobiliary outcomes	12 (8.7)	25 (1.7)	3
	Immune system outcomes	28 (20.3)	73 (5.1)	4
	Infection and infestation outcomes	4 (2.9)	8 (0.6)	0
	Injury and poisoning outcomes	0 (0)	0 (0)	0
	Metabolism and nutrition outcomes	121 (87.7)	582 (40.3)	92
	Musculoskeletal and connective tissue outcomes	2 (1.4)	2 (0.1)	1
	Outcomes relating to neoplasms: benign, malignant and unspecified (including cysts and polyps)	0 (0)	0 (0)	0
	Nervous system outcomes	6 (4.3)	16 (1.1)	2
	Pregnancy, puerperium and perinatal outcomes	0 (0)	0 (0)	0
	Renal and urinary outcomes	27 (19.6)	76 (5.3)	5
	Reproductive system and breast outcomes	0 (0)	0 (0)	0
	Psychiatric outcomes	2 (1.4)	2 (0.1)	0
	Respiratory, thoracic and mediastinal outcomes	3 (2.2)	11 (0.8)	1
	Skin and subcutaneous tissue outcomes	1 (0.7)	1 (0.1)	0
	Vascular outcomes	51 (37)	134 (9.3)	13
	Physical functioning	5 (3.6)	7 (0.5)	0
Life impact	Social functioning	5 (3.6)	6 (0.4)	0
	Role functioning	3 (2.2)	6 (0.4)	0
	Emotional functioning/wellbeing	8 (5.8)	28 (1.9)	0
	Cognitive functioning	2 (1.4)	22 (1.5)	0
	Global quality of life	4 (2.9)	5 (0.3)	0
	Perceived health status	4 (2.9)	4 (0.3)	0
	Delivery of care	30 (21.7)	60 (4.2)	4

Table 2. Summary of outcomes categorised according to the COMET taxonomy				
Core area	**Core domains**	Number of trials including one or more outcome in core domain (%)	Number of outcomes included in core domain (%)	Number of trials including as a primary outcome[a]
	Personal circumstance	0 (0)	0 (0)	0
Resource use	Economic	4 (4)	6 (0.4)	0
	Hospital	3 (2.2)	4 (0.3)	0
	Need for intervention	16 (11.6)	24 (1.7)	1
	Societal/carer burden	0 (0)	0 (0)	0
Adverse Events	Adverse events/effects	33 (23.9)	46 (3.2)	5

Table 3

Table 3. Summary of Patient Reported Outcome Measures used

		Diabetes satisfaction with treatment (DTSQ and DTSQc)	SF-36	Diabetes distress scale	Summary of diabetes self-care activities	Diabetes self-care activities scale.	8 item Morisky Medication Adherence Scale	Basic activities of daily living	Cognitive Instrumental Activities of Daily Living Scale (Cog-IADL)	Diabetes empowerment scale	Diabetes Quality of Life (DQOL)	EQ5-D	Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)	Global Clinical Dementia Rating	HFS-11 worry scale	Hospital anxiety and depression	Hypoglycaemia patient questionnaire	international physical activity questionnaire	Mini Mental State Examination (MMSE)	Montreal Cognitive Assessment scale [MoCA]	Patient Health Questionnaire-2	Subjective Memory and Cognitive Complaint (SMCC)	Well Being questionnaire Short Form (W-BQ12)	WHO-5	Number of PROMs measuring outcome
	Number of trials using PROMs	4	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Core domains	**Outcomes measured by PROM**																								
Gastrointestinal outcomes	Nausea/vomiting												X												1
	Fullness/early satiety												X												1
	Bloating												X												1
General outcomes	Pain		X									X													2
	General health		X																						1
Metabolism and nutrition outcomes	Symptomatic hypoglycaemia																X								1
	Asymptomatic hypoglycaemia																X								1
Physical	Mobility											X													1

Functioning	Physical functioning	X																1
	Energy/fatigue	X														X		2
	Physical activity											1						1
	Activities of daily living			X	X													2
	Usual activities							X										1
Social functioning	Managing the psychosocial aspects of diabetes																	0
	Quality of Life- social/vocational concerns						X											1
	Social functioning	X				X												2
	Quality of Life- general interest																X	1
Role functioning	Role limitations due to physical health	X																1
	Role limitations due to emotional problems	X																1
Emotional functioning/ wellbeing	Dissatisfaction and readiness to change					X												1
	Setting and achieving goals					X												1
	Emotional burden		X															1
	Regimen distress		X															1
	Interpersonal distress		X															1
	Physician distress		X															1
	Anxiety							X			X							2
	Depression							X			X				X			3
	Worries about diabetes						X											1
	Emotional wellbeing	X																1
	Mood																X	1
	Vitality																X	1
	Negative wellbeing															X		1
	Positive wellbeing															X		1
	General well being															X		1
	Fear of hypoglycaemia - behaviour									X								1
	Fear of hypoglycaemia - worry									X								1
Cognitive functioning	Orientation								X				X	X				3
	Registration												X					1
	Attention and calculation												X					1
	Recall												X					1

	Language										X	X		2
	Attention and concentration											X		1
	Executive functions											X		1
	Memory							X				X		2
	Visuoconstructional skills											X		1
	Conceptual thinking											X		1
	Calculations											X		1
	Judgement and problem solving							X						1
	Community affairs							X						1
	Home and hobbies							X						1
	Personal care							X						1
	Subjective memory												X	1
	Cognitive complaint												X	1
Global Quality of Life	Quality of Life -life satisfaction					X								1
	Quality of Life - diabetes impact					X								1
Perceived health status	Perceived blood glucose control	X												1
	Self-Care Activities - general diet		X	X										2
	Self-Care Activities - specific diet		X	X										2
	Self-Care Activities - medication taking		X											1
	Self-care Activities - blood glucose testing		X	X										2
	Self-Care Activities – exercise		X	X										2
	Self-Care Activities - foot care		X	X										2
	Self-Care Activities - smoking		X	X										2
	Self-Care - unspecified						X							1
	Satisfaction with treatment	X												1
	Patient knowledge of treatment for hypoglycaemia								X					1
	Medication adherence				X									1
Delivery of Care	Patient knowledge driving and hypoglycaemia									X				1

Figure

Click here to download Figure Figure 1.docx